REMARKS

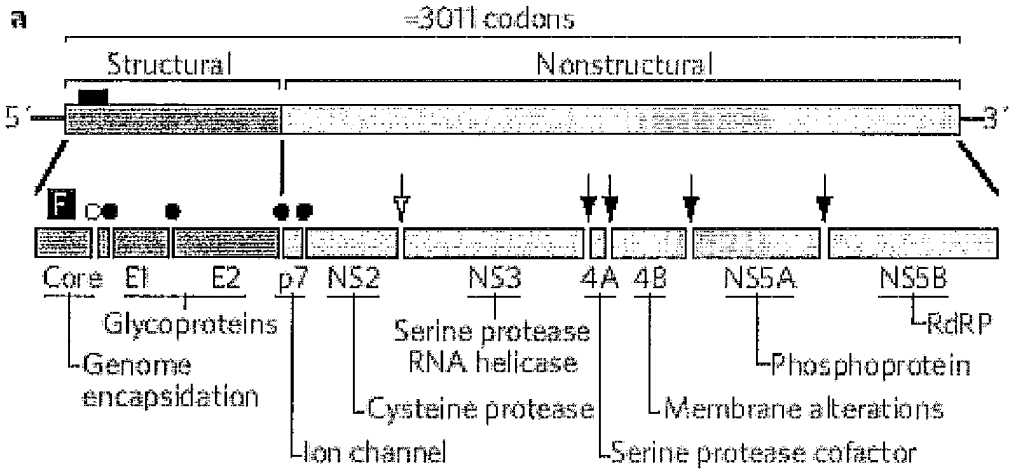
Section 103 Rejections

Claims 1-3 and 5-7 are rejected under 35 U.S.C. Section 103(a) as being unpatentable over Qian et al., Effreth et al., Zheng et al., Venugopalan et al, and Li et al., and further in view of Crooks et al. This ground of rejection is respectfully traversed.

Antiviral effect of artemisinin as described by Qian, Efferth, Zhang and Venugopalan

The examiner refers to publications by (i) Qian et al., in which activity of artemisinin is reported against the influenza virus (family Orthomyxoviridae), (ii) Efferth et al. who report activity of artesunate against HCMV and HSV-1, (family Herpesviridae), (iii) Zhang et al. who describe the effect of artemether against Bunyaviridae and (iv) Venugopalan et al. who report activity against Friend's leukemia virus (family Retroviridae). None of the viruses listed belongs to the family of the Flaviviridae, the family to which the pestiviruses and the hepatitis C virus belong. The organization of the genome as well as the replication strategy of any of these viruses listed is very different from that of the Flaviviridae. Orthomyxoviruses and bunyaviruses have negative strand RNA genomes. The genome of Orthomyxoviruses (influenza) consists of eight pieces of segmented negative sense RNA which encode 11 proteins (HA (hemagglutinin), NA (neuraminidase), NP (nucleoprotein), M1, M2, NS1, NS2 (NEP), PA, PB1, PB1-F2, PB2). Bunyaviruses have tripartite genome consisting of a large (L), medium (M), and small (S) RNA segment. These RNA segments are single-stranded, and exist in a helical formation within the virion. Besides, they exhibit a pseudo-circular structure due to each segment's complementary ends. The genome of herpes simplex virus type 1 and human cytomegalovirus (both belong to the family of the Herpesviridae) consists of a relatively large double-stranded, linear DNA genome encoding 100-200 genes. Retroviridae have a single stranded +RNA genome that is delivered in the host cell. Once in the cytoplasm the viral RNA undergoes reverse transcription to DNA after which, following transfer to the nucleus, this DNA becomes integrated in the genome of the host. By contrast Flaviviridae, to which the hepatitis C virus and the pestiviruses belong, are single stranded viruses that consist of a single stranded genome of positive polarity. Upon infection and release into the cytoplasm this viral RNA is directly translated into a long polyprotein that is further processed into unit length proteins by host cell and viral proteases. The replication strategy and the organization of the genome of Flaviviridae are very different

from the other viruses listed above. The global organization of the genome of HCV is depicted in Fig 1 (Lindenbach and Rice, Nature. (2005) 436:933-8). The organization of the genome of pestiviruses (including BVDV is very similar).



The Core protein encodes proteins that form the capsid of the virus. This core protein has no homology to the core of either orthomyxoviruses, bunyaviruses, herpesviruses or retroviruses.

The E1 and E2 genes encode the viral glycoproteins that are needed for the early stages of the infection (binding and uptake) and are not homologous to the surface (glycol)proteins of orthomyxoviruses, bunyaviruses, herpesviruses or retroviruses.

The p7 genes are believed to encode an ion channel of which the function is not well understood.

NS2 encodes a cysteine protease. Bunyaviruses and Orthomyxoviruses do not encode proteases; retroviral and herpesvirus protease are unrelated.

NS3 encodes a helicase and a serine protease, Bunyaviruses and Orthomyxoviruses do not encode proteases; retroviral and herpesvirus protease are unrelated.

NS4A is a serine protease co-factor that is unique to this group of viruses.

NS4B is believed to be involved in the formation of a membranous web on which the replication complex assembles; the protein is unique to this group of viruses.

NS5A is a phosphoprotein of which the putative function is not clear; it is unique for this group of viruses.

NS5B is an RNA dependent RNA polymerase. This polymerase is unrelated to the DNA polymerase of DNA viruses (herpesviruses), to the reverse transcriptase of retroviruses and to the RNA dependent RNA polymerases of the negative sense RNA bunya and orthomyxoviruses.

As is evident from the above, the reported activity of artemisinin and/or artimeter against a selection orthomyxoviruses, bunyaviruses, herpesviruses and retroviruses actually teaches away from any antiviral activity against HCV and pestiviruses. This is further supported by the well-established knowledge in the art that commercial available antiviral medicines do have an effect against all viruses - for example, acyclovir is active against herpes viruses, but it cannot cure/affect other viruses such as hepatitis B or influenza. The same is true with respect to known antiviral vaccines - for example, Twinrix will protect against hepatitis A virus and hepatitis B virus, but not against hepatitis C.

Artemisinin augments cell-mediated immunity as described by Crooks and Qian

Qia et al. report that the immunologic effect of artemisinin simulates that of cyclophosphamide. The relatively selective suppression of B-lymphocytesby cyclophosphamide can enhance the function of T lymphocytes. Qian et al. suggest that artemisinin may exert augmentative action on cell-mediated immunity.

Crooks et al. report that compounds with an immunomodulating activity are useful in treating diseases, such as HSV-1, HSV-2, HIV, CMV and VZV.

In cell-based antiviral assays, no immuno cells are encountered. Hence, cell-mediated immunity does not play any role in these assays, with the result that the observed antiviral activity in these assays is not attributable to a possible cell-based immunomodulating effect of the compound. Therefore, the observed antiviral effect of artemisinin against BVDV is due to other mechanisms.

Additionally, artemisinin did not show any antiviral effect in cell-based antiviral screenings against HSV-1, HSV-2, HIV-1, HIV-2, Vaccinia Virus, CMV Davis, CMV AD-169, VZV OKA and VZV YS.

For these reasons, a possible immunomodulating effect of artemisinin does not teach, suggest, or motivate those skilled in the art to carry out these cell-based antiviral screenings, because this effect is not visible in these assays..

The Section 103(a) rejections of claims 1-3 and 5-7 should be reconsidered and withdrawn.

Accordingly, the purpose of the claimed invention is not taught nor suggested by the cited references, nor is there any suggestion or teaching which would lead one skilled in the relevant art to combine the references in a manner which would meet the purpose of the claimed invention. Because the cited references, whether considered alone, or in combination with one another, do not teach nor suggest the purpose of the claimed invention, Applicant respectfully submits that the claimed invention, as amended, patentably distinguishes over the prior art, including the art cited merely of record.

Based on the foregoing, Applicant respectfully submits that its claims 1-3, and 5-7 are in condition for allowance at this time, patentably distinguishing over the cited prior art. Accordingly, reconsideration of the application and passage to allowance are respectfully solicited.

The Examiner is respectfully urged to call the undersigned attorney at (515) 288-2500 to discuss any remaining issues that may exist or arise.

Respectfully submitted,

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